

Pasireotide (SIGNIFOR® LAR) **National Drug Monograph** **Abbreviated Review Addendum** **October 2015**

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs and abbreviated reviews is to provide a focused drug review for making formulary decisions. Updates will be made when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

This addendum to the original abbreviated review for pasireotide in Cushing's disease ([PBM MAP VPE Abbreviated Reviews](#)) provides information on the approval of pasireotide LAR for acromegaly.

Introduction¹⁻⁷

Pasireotide (SIGNIFOR LAR) injectable suspension, for intramuscular (IM) use was FDA approved December 2014 for patients with acromegaly who have had an inadequate response to surgery and/or in whom surgery is not an option.

Acromegaly is a rare disorder, with an estimated three to four per million people who develop the disease each year. It is estimated that approximately 15,000 people in the U.S. and Canada have acromegaly, with approximately 400 patients with the diagnosis receiving care in the Veterans Health Administration.

Patients with acromegaly are at an increased risk of mortality (overall standardized mortality ratio 1.48) associated with cardiac, respiratory, and diabetic complications. In one evaluation of over 400 patients, an increase in mortality was attributed to an elevated growth hormone (GH) level (i.e., above 2 mcg/L). In addition, GH levels < 2.5mcg/L are an independent predictor of improved survival. Prior to available treatments, the survival of patients with acromegaly was decreased by 10 years compared to a control population. Symptoms may include abnormal growth of bones in the hands, feet, nose, and jaw; joint pain, paresthesias, excessive perspiration; glucose intolerance or diabetes; and enlargement of organs including heart, liver, kidneys, and spleen. Acromegaly is a disorder most often resulting from an increase in production of GH by tumors of the anterior pituitary gland. The secretion of GH is induced by GH-releasing hormone (GHRH) and suppressed by somatostatin. Growth hormone stimulates the production of insulin-like growth factor-1 (IGF-1) by activating GH receptors in the liver. Recent recommendations are to target a goal of age-normalized IGF-1, and GH < 1.0 mcg/L.

In patients who are surgical candidates and depending on the characteristics of the tumor, first-line therapy for treatment of acromegaly due to anterior pituitary gland tumors includes surgical resection of the tumor. Since surgery is not curative in all patients (remission in: 72% with microadenoma; 50% with macroadenoma), additional treatment is often required. Radiation therapy may be considered in patients with tumor recurrence or persistence with an inadequate response or intolerance to pharmacotherapy. Pharmacotherapeutic options include the use of somatostatin receptor ligands, GH receptor antagonists, or dopamine receptor agonists.

Lanreotide and octreotide, somatostatin analogs selective for the receptor subtypes SST2 and SST5, inhibit the secretion of GH resulting in decreased levels of IGF-1, with reports of GH levels < 2.5mcg/l in 48 to 68% of patients, and normalized IGF-1 levels in approximately 50% of patients. Pasireotide is a multi-receptor ligand somatostatin analog that has a high binding affinity for SST1, 2 and 3, with a binding affinity for SST5 that is reported to be 40 times higher than octreotide. All three of the available somatostatin analogs are FDA approved for treatment of patients with acromegaly. Pegvisomant is a GH analog that acts as a GH receptor antagonist and is approved for acromegaly in patients with inadequate response to or who are not candidates for surgery or radiotherapy. It is also used in patients who do not respond to other medical therapy. Dopamine agonists such as bromocriptine have also been used in the treatment of patients with acromegaly; although, this treatment is recommended in more mild disease or as adjunctive therapy.

Somatostatin Analog ^{1,3-6}	FDA Indications*	VANF
Octreotide acetate inj (IV or SC)	Acromegaly	Yes
Octreotide acetate inj, susp, SA (Depot LAR) (IM; should be administered by a trained HCP)	Carcinoid tumors (management of carcinoid syndrome – diarrhea/flushing) VIP-secreting tumors (management of profuse watery diarrhea)	Yes
Lanreotide inj, susp, SA (Depot) (deep SC; should be administered by a HCP)	Acromegaly GEP-NET to improve PFS	Yes
Pasireotide inj (SC)	Cushing's Disease (Pasireotide)	No
Pasireotide powder, inj (LAR) (IM; must be reconstituted and administered by a trained HCP)	Acromegaly (Pasireotide LAR)	No

GEP-NET=gastroenteropancreatic neuroendocrine tumors; HCP=healthcare professional/provider; IM=intramuscular; IV=intravenous; LAR=long-acting repeatable (octreotide), long-acting release (pasireotide); PFS=progression free survival; SC=subcutaneous; VANF=VA National Formulary; VIP=vasoactive intestinal peptide

*FDA indications for all formulations unless stated otherwise

Efficacy (Acromegaly)^{1,8,9}

Review of Efficacy^{1,8,9}

- The approval for pasireotide LAR in patients with acromegaly was based on two clinical trials: one in treatment-naïve patients;⁸ and another in patients with inadequate control on another somatostatin analog.⁹
- A multicenter, randomized, double-blind trial was conducted in 358 patients with acromegaly (GH > 5 mcg/L, or GH nadir ≥ 1 mcg/L after an oral glucose tolerance test, and IGF-1 above the upper limit of normal [ULN]). Patients had not received prior medical therapy and were stratified based on whether they had prior pituitary surgery. Patients received either pasireotide 40 mg LAR or octreotide 20 mg LAR, every 28 days; titrated to 60 mg or 30 mg, respectively, at 3 or 7 months, if indicated (mean GH ≥ 2.5 mcg/L and/or IGF-1 > ULN). Mean baseline GH was 21.9 mcg/L and 18.8 mcg/L, and mean standardized IGF-1 was 3.1 and 3.1 times ULN, in the pasireotide LAR and octreotide LAR treatment groups, respectively. The dose was increased in 50.6% of patients on pasireotide LAR and in 67.6% on octreotide LAR during the 12 months of treatment. It was noted that 31.0% of patients treated with pasireotide LAR and 22.2% of patients receiving octreotide LAR did not have an increase in their dose as per consideration for patients not biochemically controlled per protocol⁸ (per the product information, it was also noted that the maximum dose of octreotide LAR approved in the U.S. was not used in the trial; although, the majority of patients were treated with the usual dose of octreotide LAR used for acromegaly).¹ The primary endpoint of proportion of patients with GH < 2.5 mcg/L and normal IGF-1 at 12 months was achieved in 31.3% of patients treated with pasireotide LAR compared to 19.2% of patients in the octreotide LAR treatment group (P=0.007). When data were evaluated according to post-surgical patients (42%) and de novo (58%), the primary endpoint for pasireotide LAR vs. octreotide LAR was statistically significantly different in the postsurgical group (OR 2.34; 95% CI 1.14 to 4.79) but not in the de novo group (OR 1.65; 95% CI 0.85 to 3.23). Completion of 12 months of treatment was documented in 80.1% receiving pasireotide LAR and 85.7% treated with octreotide LAR. Discontinuation due to adverse events was reported in 8.0% of patients treated with pasireotide LAR compared to 3.3% of patients in the octreotide LAR treatment group. The most common adverse events reported for pasireotide LAR and octreotide LAR, respectively, were: mild to moderate diarrhea (39.3% vs. 45.0%), cholelithiasis (25.8% vs. 35.6%), headache (18.5% vs. 25.6%), and hyperglycemia (28.7% vs. 8.3%). The study was funded by Novartis Pharma AG.⁸

Study Results⁸

Endpoints	Pasireotide LAR N=176 (%)	Octreotide LAR N=182 (%)	Odds Ratio (95% CI)	P value
GH < 2.5 mcg/L and normal IGF-1 ^a	31.3	19.2	1.94 (1.19 to 3.17)	0.007
GH < 2.5 mcg/L	48.3	51.6		0.54
Normal IGF-1	38.6	23.6		0.002

^a Primary endpoint

- In another multicenter trial, 198 patients with uncontrolled acromegaly (GH > 2.5 mcg/L and IGF-1 > 1.3 times ULN) despite treatment with lanreotide 120 mg autogel (Depot) or octreotide 30 mg LAR monotherapy for ≥ 6

months were randomized to pasireotide LAR 40 mg, 60 mg or active control (continued dose lanreotide or octreotide, respectively) every 28 days for 24 weeks. Investigators were blinded only to pasireotide dose allocation. Mean baseline GH was 17.6 mcg/L, 12.1 mcg/L, and 9.5 mcg/L in the pasireotide 40 mg, 60 mg, and active control group, respectively. Mean IGF-1 was 2.6, 2.8, and 2.9 times ULN, in the pasireotide 40 mg, 60 mg, and active control group, respectively. The primary endpoint of number of patients with GH < 2.5 mcg/L and normal IGF-1 at 6 months was achieved in 10 (15%) of patients treated with pasireotide 40 mg LAR, 13 (20%) treated with pasireotide 60 mg LAR, compared to no patients in the active control group. Patients with at least one adverse event included 92% treated with pasireotide 40 mg LAR, 85% on pasireotide 60 mg LAR, and 74% receiving active control. Serious adverse events were reported in 10% of patients treated with pasireotide 40 mg LAR, 3% on pasireotide 60 mg LAR, and 5% of patients in the active control group. The most common adverse events reported in the pasireotide 40 mg LAR, pasireotide 60 mg LAR, and active control groups, respectively, were: hyperglycemia (33%, 31%, 14%), diabetes (21%, 26%, 8%), and diarrhea (16%, 19%, 5%). The study was funded by Novartis Pharma AG.⁹

Study Results⁹

Endpoints	Pasireotide 40 mg LAR N=65 (%)	Pasireotide 60 mg LAR N=65 (%)	Active control group ^b N=68 (%)	P value (Absolute difference Pasireotide vs. Control)
GH < 2.5 mcg/L and normal IGF-1 ^a	10 (15)	13 (20)	0	0.0006 (40 mg); <0.0001 (60 mg)
GH < 2.5 mcg/L	23 (35)	28 (43)	9 (13)	0.0024 (40 mg); 0.0001 (60 mg)
Normal IGF-1	16 (25)	17 (26)	0	0.0006 (40 mg); <0.0001 (60 mg)

^a Primary endpoint

^b Lanreotide 120 mg Autogel (Depot) or Octreotide 30 mg LAR

- Overall, there is moderate quality of evidence for the use of pasireotide LAR for the management of patients with acromegaly to control biochemical abnormalities of IGF-1 and GH levels, and in patients with inadequate control on previous treatment with other somatostatin analogs (Refer to Appendix A).

Safety¹

- Warnings and precautions include:
 - Hyperglycemia and diabetes: may be severe; periodically monitor glucose during therapy (evaluate more closely during initiation, discontinuation, or dose adjustment), treatment for diabetes may be indicated
 - Bradycardia and QT prolongation: use with caution in patients at increased risk; evaluate electrocardiogram and electrolytes prior to and periodically during therapy
 - Liver function test elevation: evaluate prior to and during treatment
 - Cholelithiasis: monitor periodically
 - Pituitary hormone deficiency: periodically monitor and treat as indicated
- Refer to the product information for details on safety, as well as dosing and administration, and other information on the use of pasireotide LAR.¹

Projected Place in Therapy

- Treatment with pasireotide LAR was reported to reduce the primary endpoint (GH < 2.5 mcg/L and normal IGF-1) in a greater percentage of patients with acromegaly than octreotide LAR in one trial, and in another trial of patients with acromegaly inadequately controlled on previous therapy with octreotide LAR or lanreotide Depot. In both trials, adverse events related to hyperglycemia or diabetes occurred more frequently in the pasireotide LAR treatment groups.
- Somatostatin analogs are generally recommended for the management of patients with acromegaly who have inadequate control after surgery, or who are poor surgical candidates. In patients who have an inadequate response to a somatostatin analog (e.g., lanreotide, octreotide are available on the VA National Formulary), pegvisomant or a dopamine agonist has been recommended as adjunct therapy. Pasireotide LAR may be another treatment option in patients with inadequate control on treatment with lanreotide or octreotide; taking into consideration efficacy, safety and side effects, patient convenience, and cost.

References

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9. Gadelha MR, Bronstein MD, Brue T, et al.; Pasireotide C2402 Study Group. Pasireotide versus continued treatment with octreotide or lanreotide in patients with inadequately controlled acromegaly (PAOLA): a randomised, phase 3 trial. *Lancet Diabetes Endocrinol* 2014;2:875-84.

Appendix A: GRADEing the Evidence

Designations of Quality

<u>Quality of evidence designation</u>	<u>Description</u>
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High	Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes (2 consistent, higher-quality randomized controlled trials or multiple, consistent observational studies with no significant methodological flaws showing large effects).
Moderate	Evidence is sufficient to determine effects on health outcomes, but the number, quality, size, or consistency of included studies; generalizability to routine practice; or indirect nature of the evidence on health outcomes (1 higher-quality trial with > 100 participants; 2 higher-quality trials with some inconsistency; 2 consistent, lower-quality trials; or multiple, consistent observational studies with no significant methodological flaws showing at least moderate effects) limits the strength of the evidence.
Low	Evidence is insufficient to assess effects on health outcomes because of limited number or power of studies, large and unexplained inconsistency between higher-quality studies, important flaws in study design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes.

Please refer to Qaseem A, et al. The development of clinical practice guidelines and guidance statements of the American College of Physicians: Summary of Methods. *Ann Intern Med* 2010;153:194-199.